## REMARKS

Claims 1-19 are pending, with claims 7, 8, 12, 13 18 and 19, being withdrawn from consideration. Claims 1-13 and 15-17 are amended herein. A substitute specification and new and replacement drawings are provided herewith. No new matter is introduced by way of the amendments to the claims, the substitute specification or the new/replacement drawings. Applicants respectfully request entry of the amendements to the claims, specification and drawings.

Double patenting

Claim 1 is provisionally rejected over claim 10 of copending application no. 10/535047. To the extent that the Examiner believes that this rejection should be maintained with respect to the amended claims, Applicants respectfully request that the rejection be held in abeyance until such time as one or the other application is in condition for allowance or until the double patenting rejection is the only rejection remaining in the application.

Claims 1-6, 9-11 and 15-17 are enabled as required by 35 U.S.C. § 112, first paragraph.

Claims 1-6, 9-11 and 15-17 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Without agreeing or disagreeing with the Examiner's contention, Applicants have amended the claims rendering the rejection moot.

Claims 1-5, 15 and 16 are non-obvious

Claims 1-5, 15 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious in view of Chien *et al.* (US 6261764, "Chien") in view of Glenn *et al.* (US2006/0199174, "Glenn") or Shah *et al.* (US 6727092, "Shah"). To the extent that the rejection is maintained with respect to the amended claims, Applicants traverse.

Under 35 U.S.C. § 103, a patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support he legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.* (550 U.S. ___, 127 S. Ct. 1727, 2007, 82 USPQ2d 1385, 1396).

Where the Examiner alleges that the claimed invention is a combination of prior art elements according to known methods, the Examiner must articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference:
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
> Federal Register Vol. 72, No. 195: 57256, at 57529.

"If any of these findings cannot be made, then this rationale *cannot* be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.* (emphasis added)

Thus, a proper rejection under 35 USC § 103 requires that the Examiner 1) identify prior art that differs from the claimed subject matter only in a way that would have been obvious at the time the invention was made; and 2) to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

The current claims are directed to immunogenic compositions that include a first expression cassette comprising a polynucleotide sequence that encodes an HCV Core protein and a second expression cassette comprising a polynucleotide sequence that encodes at least one other HCV protein, wherein the first and second expression cassettes cause expression of the Core protein and the at least one other HCV protein within the same cell, wherein the first expression cassette encoding the Core protein is in a cis location downstream of the second expression cassette that encodes at least one of the other HCV proteins. Such immunogenic compositions are demonstrated to elicit an immune response specific for HCV when administered to a subject *in vivo*.

The currently claimed immunogenic compositions all share a common technical feature, that is a first expression cassette comprising a polynucleotide sequence encoding the HCV core protein that is located downstream from a second expression cassette

encoding at least one other HCV protein. Such immunogenic compositions are both novel and non-obvious with respect to the cited references, as explained in more detail below.

Chien concerns buffers for stabilising antigens, specifically HCV antigens, for use in the field of immunoassays, specifically anti-HCV immunoassays (column 1, field of invention). The Examiner has not pointed to any portion of this document that discloses the use of HCV antigens in immunogenic compositions, let alone provides evidence in relation to the specific HCV antigens of the invention as immunogenic compositions that are capable of eliciting an immune response against HCV *in vivo*.

Chien discloses a number of HCV antigens that the diluents or buffers of the invention can be used with in manual or automatic assays (column 4, lines 48-54). Included in this list is MEFA-6, which has been highlighted by the examiner. The MEFA-6 cassette (note that this is a single cassette) contains epitopes from the core, envelope, NS3, NS4 and NS5 regions of the HCV polyprotein (Column 5, lines 12-15) and results in the production of a single multiple-epitope fusion antigen. Chien does not, however, disclose or suggest a first expression cassette encoding the HCV core protein that is downstream from a second expression cassette encoding at least one other HCV protein.

Glenn (US2006/0199174) discloses methods and compositions for identifying agents for treating infection by viruses, such as HCV, that encode a nucleotide-binding NS4B protein. This application discloses that the HCV NS4B polypeptide contains a nucleotide binding motif, can hydrolyse nucleotides, and can bind RNA in the presence of nucleotide ([0054] of US2006/0199174).

It is stated in [0055] of US2006/0199174 that, in general, the methods of the invention for identifying an anti-viral agent involve contacting a polypeptide having an NS4B nucleotide binding motif with a candidate agent, and determining the effect of the candidate agent on a nucleotide binding activity, a nucleotide hydrolysing activity, or a nucleotide-dependent RNA binding activity of the polypeptide. Accordingly, the focus of US2006/0199174 is on anti-viral agents which target the nucleotide binding motif of NS4B. Paragraph [0113] of US2006/0199174 mentions immune response-stimulating compositions which contain virus particles containing polynucleotides encoding polypeptides having an NS4B nucleotide binding motif. However, nowhere are

immunogenic compositions containing the HCV core protein and at least one other HCV protein suggested.

Paragraph [0073], to which the examiner refers, concerns vectors of the invention and simply states that "*vectors, including single and dual expression cassette vectors are well known in the art*" in general terms. The vectors discussed in [0073] are for expressing the NSB4 nucleotide binding motif polypeptides of the invention discussed in [0064].

The entire focus of the Shah patent (US6727092) is on HCV diagnostic tests, specifically methods for the simultaneous detection of HCV antigens as well as antibodies produced in response to HCV antigens (column 1, technical field), unlike the present invention which is directed to immunogenic compositions that are capable of eliciting an HCV specific immune response *in vivo*.

Example IV of US6727092 concerns the construction of recombinant antigens for use in an HCV core antibody/antigen combination assay, specifically the construction of recombinant HCV antigens that contain the 33c region of HCV (amino acids 1192-1457 – NS3) tethered to a core region of the virus. The template used for preparing this construct was a plasmid containing a bacterial codon-optimised sequence of amino acids 1192-1457 (NS3), followed by amino acids 1-150 (core) from the H strain of HCV with two non-HCV coding amino acids separating the two sequences (column 17, A. Background).

It is clear, however, that a single plasmid was used to express the recombinant antigen with the coding sequences for NS3 and core being under the control of a single promoter, *i.e.*, within a single expression cassette. Shah *et al.*, therefore, do not disclose a dual promoter construct, as required by the present invention, wherein a first expression cassette encoding the HCV core protein is downstream from a second expression cassette encoding at least one other HCV protein, as was alleged in the paragraph spanning page 2 of the office action dated 17th January 2008. A definition of an "expression cassette" can be found on page 16 of the present application, at lines 6-9, where it is stated that "*an expression cassette is an assembly which is capable of directing the expression of the sequence or gene of interest. The expression cassette comprises control elements, such as a promoter which is operably linked to the gene of interest.*"

There is simply no incentive for the skilled person from reading any of these prior art documents to prepare an immunogenic composition/vaccine comprising a polynucleotide sequence encoding HCV antigens by means of more than one expression

cassette. In the unlikely event that the skilled person would consider using more that one expression cassette for expressing the various HCV antigens, there would be no reason to select the core protein, as opposed to any other HCV protein, as a protein that should be expressed in an expression cassette downstream of an expression cassette encoding another HCV protein. There would have been no expectation that the order in which cassettes are inserted into a vector should have any effect on the expression from either cassette.

Furthermore, the particular order in which the cassettes are inserted in the vector have been shown to yield surprising and beneficial results. That is, arrangement of the first expression cassette encoding the Core protein is in a cis location downstream of the second expression cassette that encodes at least one of the other HCV proteins results in the alleviation of the substantial reduction in expression of non-core HCV proteins when their respective cassettes are positioned downstream of a core containing cassette (as shown in Example 6). Accordingly, the subject matter of claims 1-5, 15 and 16 is non-obvious, and Applicants respectfully request that the rejection be withdrawn.

## Conclusion

Applicants respectfully submit that claims 1-6, 9-11 and 15-17 are allowable in view of the above remarks. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is requested to call the undersigned at the number below prior to the preparation of any further written action. Applicants reserve the right to prosecute subject matter in the originally filed claims, or any other claims supported by the specification in one or more continuing patent applications.

Respectfully submitted,

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